REMARKS/ARGUMENTS

Presently claims 16-35 stand pending. Claims 16, 19 and 27 are amended herein; entry of these amendments is respectfully requested. No new matter is added by these amendments. After entry of these amendments, claims 16-35 remain pending in this application.
The following remarks and arguments are provided, and address objections and rejections in the sequence the latter are provided in the Office action.

Rejection of Claims Under 35§ USC 112

Claims 16-22 and 27 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. Generally, it is alleged that the claim(s) contain(s) subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 16, the sole independent claim of the rejected claims 16-22 and 27, has been amended, and it is believe that this amendment is effective to overcome this rejection. However, the following arguments also are provided, and they may further convince the Patent Office that the present claims are enabled.

First, it is noted that claim 16 is amended to specify that the treatment is carried out on "an individual in need of." This in part is provided to clarify that the focus of the claims is on human individuals in need of the medicament, and the further listing of states to be treated, initially classified by the three groups at the end of claim 16 and further specific in various dependent claims, should make clear that the method of treatment is not to be extended to "myriad mammalian subjects." It is clear that these states are concerns for human individuals, although recognized laboratory species were used for demonstration of effectiveness. From a standpoint of utility, practicality, and treatability (e.g., the difficultly of compliance for repeated treatments for a bear in the woods), it is not logical to extend the scope of possible subjects to "myriad mammalian subjects" and the amendment herein is intended to clarify that. As for support in the

specification, the word "individual(s)" is used in example 7 of the filed application. Also, the word "patient" also is used in many passages of the application, and it is clear that the use of patient in the application refers to and is essentially synonymous with "individual" as used in the specification and claims.

By so limiting the individual in need of the medicament, this greatly reduces the quantity of experimentation allegedly needed to arrive at the dosages that are most effective in treating the listed states. Also, claim 16 is amended to include a specific dosage range, and this clearly reduces the quantity of such experimentation to a quantity that clearly is not undue. Accordingly, on this basis alone it is respectfully requested that this basis for the enablement rejection be withdrawn.

Further to the arguments and rejections based on re Wands (8 USPQ2d, 1404), the following observations are also placed on the record for consideration:

1) The quantity of experimentation necessary is not a parameter in itself, but is the consequence of all the other points.

2) The amount of direction or guidance presented: The different routes and types of administering the medicament and the amounts of active agent to be given for each type of administration are properly disclosed from pages 9 to 12, specifically in paragraph 0031 which bridges pages 11 and 12 of the filed application.

3) The presence or absence of working examples: There are four examples of specific pharmaceutical formulation and three examples of specific pharmaceutical or cosmetic application.

4) The nature of the invention: The invention does not belong to an emerging or pioneer field. The technical field is the classical pharmaceutical field and the skilled person is supposed to be supported by an extensive "common general knowledge".

5) The state of the art: As to the testing of various medicaments for the diseases of interest, the prior art has proven the utility of animal and human models for checking scleroderma, skin aging and hair growth. These model systems, which are widely accepted, are available as indicated in the examples, and can reduce the quantity of experimentation.

6) The relative skill of those in the art: See previous points (4) and (5). The relatively high level of skill and knowledge in the art reduces the level of experimentation needed once the concept was formed by the inventors, and thus reduces the need for experimentation, and corresponding argues in favor of there being no undue experimentation to reach the scope of the claims, particularly as now amended.

7) The predictability or unpredictability of the art: The reliability of the affirmed PLGF-1 activity is unambiguously shown on two animal models (examples 5 and 6) and on human subject(example 7). These examples show the efficacy of the very mechanism underlying the pharmaceutical or cosmetic effects, namely that PLGF-1 brings about an improved angiogenesis, which contributes to improve alterations of cutaneous or subcutaneous connective tissues, such as the increased sclerosed collagen typical of scleroderma. This fundamental proof of underlying mechanism reduces the unpredictability as to the present invention in particular, and therefore argues for no undue experimentation to reach the scope of the claims, particularly as now amended.

8) The breadth of the claims: Claim 1 is now limited to human individuals and to specific amounts of active principle. Consequently, far less experimentation is called for, and this level of experimentation is not undue.

Weighing the factual considerations established in regard to all of these factors, and in view of claim 16 as amended, the invention should be considered not requiring undue experimentation to practice the invention, and should be determined to meet the requirement of enablement.

Further to the enablement issue, and to proof of the conceptual framework of the invention, the last paragraph of example 7 shows that the treatment with PLGF-1 results in an improved

perifollicolar vascularization. This is considered by the skilled person as a proof of a boosting effect to the hair growth, regardless of the reason of the hair loss.

Finally as to this matter, as to the statement in the Office action regarding the difficulty of obtaining effective dosage levels to properly treat a condition, first, it is recognized that dosages across a range may be determined for the population in general, and that there often is, depending on the condition and differences in individuals and their habits, a fine-tuning to reach a proper dosage. It is not proper to consider this type of dosage adjustment to be "undue experimentation." Further, the addition of a range of specific amounts to claim 16 means that any treatments are within this range, and the establishment of proper general or individual-specific doses for a particular condition do not rise to "undue experimentation" within this framework. This is particularly the case now that claim 16 also has been limited to administering to an individual rather than to "myriad mammalian subjects."

Reconsideration and withdrawal of the rejection of claims 16-22 and 27 under 35 U.S.C. 112, first paragraph, are respectfully requested.

Claim 19 stands rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant has amended the claim, removing the word "particular" (added in an amendment mailed 07/27/2006) as this claim, prior to the addition of this word, has withstood at least two patentability considerations by the Patent Office without rejection. This is believed to render this rejection moot. It is noted that this claim is meant to distinguish from natural hair loss, and recites a number os states (which are found in the specification, paragraph 0029) that in this claim fall into a group identified as pathological hair loss. The amendment to remove the word "particular" does not alter the scope of this claim, as this rejection is considered a technical rejection owing to Patent Office's interpretation of "particular" as requiring specific particular states within the listed states. However, this is not the case.

Rejection of Claims under 35 USC § 102

Claims 30-35 stand rejected again under 35 USC 102(b) as being allegedly anticipated by Ziche et al.

The Office action maintains that the solution disclosed by Ziche is suitable as a topical composition therefore it is equivalent to the compositions of the invention, the intended pharmaceutical purpose not being a limiting element of the protection.

However, the difference between the Ziche solution and the present compositions is not to be seen in the "intended purpose" but is the amount of active agent comprised in the compositions as currently presented.

Claim 30 seeks protection for a pharmaceutical composition comprising PLGF-1, essentially in dimeric form, as active principle in an amount of 0.1 to 10 milligrams per gram of topical composition, whereas Claim 31 seeks protection for a cosmetic composition comprising from 0.01 mg (10^4 ng) to 0,09 mg ($9x10^4$ ng) per gram of composition.

The Office action also apparently argues that the units of dosage recited in the claims would not be relevant. In other words, there appears to be a disregard the amount of active principle in the medicament when this is provided as a limitation of the claim. Yet, the amount of the active principle is the second essential characteristic of any medicament, the first being the principle (i.e., the chemical composition) itself.

Ziche discloses the use of PLGF-1 in amounts completely different from those of the present invention.

As evident from the sections "*PGF-1 Promotes Angiogenesis in ARC*" on page 518, or "*PGF-1 Promotes Angiogenesis in Embryonic CAM*" on page 519, or "*Chemotactic Effect*" on page 521, this document discloses compositions in form of implants or solutions comprising no more that 200 ng/pellet (i.e. dosage-unit) or 180 ng/ml solution.

On the contrary, the composition of claims 30 comprises amounts of active agent, which vary from 0.1 mg (10^5 ng) to 10 mg (10^7 ng) per gram of topical composition

Thus, the highest amounts disclosed by Ziche ($2x10^2$ ng/pellet or $1,8x10^2$ ng/ml) are dramatically much lower (at least by a factor 10^2) than the amounts defined in claim 30.

The same prove valid for claim 31, the amounts disclosed therein ranging from 0.01 mg (10^4 ng) to 0,09 mg ($9x10^4$ ng) per gram of composition.

Therefore the rejection for lack of novelty of claims 30 and 31 and 32 to 35 would appear to be untenable in view of the above analysis when considering the requirements for a 35 USC 102(b) rejection. Accordingly reconsideration and withdrawal of the rejection of claims 30-35 rejected, again, under 35 USC 102(b), are respectfully requested.

Rejection of Claims under 35 USC § 103

Claims 16-22 and 23-26 stand rejected again under 35 USC 103(a) as being allegedly unpatentable over Ziche et al. in view of Failla et al.

To summarize, the diseases object of the present invention are all related to alterations of the **connective tissues** and are characterized by fibroblast activation and excessive production and deposit of sclerotized collagen with formation of fibrosis and calcification zones (see filed description page 6 lines 6 to 15, or more generally paragraphs 0017-0029). In contrast, the references cited in the rejections address physiological changes in normal tissues, wound healing, or other conditions which differ from the states for which treatment is claimed herein. Appreciation of such differences, as well as other differences in the claim limitations, may lead to recognition of the patentability of the claims.

Ziche, which has already been thoroughly discussed in previous responses, which are incorporated by reference into this discussion, discloses the ability of PLGF-1 to elicit

angiogenesis in two animal models: the rabbit cornea and the chicken chorioallantoic membrane. This is a simple biological activity developed on normal (healthy) rabbit cornea or chorioallantoic membrane, which are **endothellial tissues**. This biological activity cannot be confused with a pharmacological, therapeutic effect, that necessarily implies the capability of correcting and recovering an abnormal situation. This capability is not recognized in Ziche's article, which is completely silent on any envisageable therapeutic application of PLGF-1, let alone on the specific therapeutic treatment of the diseases cited in the present application.

Moreover the activity reported by Ziche concerns endothelial cells, not connective tissues. **Neither cornea nor the chorioallantoic membrane are made of connective tissues, let alone connective tissues comprising deposit of sclerotized collagen with formation of fibrosis and calcification zones .**

Also, Ziche does not disclose or suggest that the pathological picture treated according to the invention is caused by or correlated to a deficient angiogenesis in the connective tissues. Nor could the skilled reader find any suggestion in Ziche's teaching that giving heterologous PLGF-1 would improve vascularization in sclerotized connective tissues, as observed in healthy cornea, and still less that improved vascularization, if any, would be able to restore the healthy state of the sclerotized connective tissues.

Even assuming, for the sake of argument, that the evidence reported by Ziche would suggest that PLGF-1 could be used to treat scleroderma and the other states, then the skilled person, in following such a "suggestion", would have used PLGF-1 in such a low concentration (the one used by Ziche) that he/she would have observed no effect at all. Nor could the skill person find in this prior art any hint, motivation or reason to increase the amount of PLGF-1, overtaking the amount disclosed by Ziche.

In other words, Ziche does neither suggest that PLGF-1 could be used for the therapeutic application according to the present invention, nor the suitable amounts to appreciate any effect.

On these bases alone as to Ziche, individually or in any combination, the rejection of these claims should be withdrawn.

As to the Failla et al. reference, the rejection relies on a passage of the abstract in which Failla indicates that native PLGF is induced in human keratinocytes during wound healing and demonstrates that PLGF plays "a role" in the neoangiogenesis process associated with wound repair.

The Office action seems to consider (page 9) that the expression in claim 16 "pathological alterations of the ...tissue" encompasses "wound", which is generally recognized to be an acute alteration of the cutaneous tissues (note that a mark on a body where long ago there had been a wound is called a scar, not a wound). Toward addressing this concern of the Patent Office, claim 16 as amended no longer includes the word "alteration". Therefore this aspect of the rejection appears moot, and further aspects of the clear distinction between wound and claimed states follow.

The examiner seems also consider "wound" equivalent to "earlier skin aging", because earlier skin aging is due to exposure to aggressive agents or solar irradiation which upon extensive exposure may also cause skin wound or skin burn. This argument is untenable, because, as well known, solar irradiation may also cause skin tumor. By following the examiner's argument, also a skin tumor would be equivalent to skin aging, which seems really illogical and ultimately untenable.

In fact, "earlier skin aging", "wounds" or even "tumor" are all completely different and independent states and only the former, but not the others fall within the scope of protection conferred by claim 16.

The person skilled in the art knows very well that the two states "earlier skin aging" and "wounds" are completely independent. As but one proof of this, a "young" skin remains young also upon and after an incident of a solar wound or burn. After healing the skin return to its

original young condition. In fact, "wound" is an acute state, which normally does not leave irreversible traces.

On the contrary "skin aging" is a chronic state caused from the continuous exposure to aggressive agent and resulting in a excessive production and deposit of sclerotized collagen. As for an analogy, assume that a first inventor discovered that a composition ameliorated free radical damage in cells at a particular low dosage. Assume a later inventor discovered that at substantially higher doses the same composition treated a type of cancer when applied topically to the cancer, which was believed often (or exclusively) in part the result of chronic free radical damage, and in part also due to many other factors, including genetic, immunologic, dietary, etc.. If there were no teaching, motivation or suggestion in the first inventor's disclosure as to the possible utility to use the composition at higher doses for this cancer type, which is one of the many results of free radical damage, then it appears that the first inventor's disclosure is not an appropriate reference to use for an obviousness rejection. Similarly, there appears no valid basis, in view of the above, to use the Failla reference in the present rejection.

Therefore the teaching of Failla that PLGF-1 would appear to have a role in healing wounds nevertheless would not be able to suggest that PLGF-1 could also be used according to the present invention.

The second point is that the Office action appears to interpret that Failla discloses the use of PLGF in the healing wounds. Applicants respectfully assert that this is incorrect.

In fact, while indicating a role of PLGF in cutaneous wound repair process, Failla does not demonstrate that PLGF has any active function in the healing. Said in other words, the reference fails to show that the induced PLGF is the **factor causing the healing rather than simply being a side effect of the wound or a marker**. By way of example, there are known benign tumors characterized by the release of thyroid hormones. The higher level of circulating hormones are neither the cause of the tumor nor a repair factor for the tumoral damages, but simply a side effect or a marker.

Finally, Failla does not show that the PLGF induced in vivo actually is PLGF type 1, and not PLGF-2, PLGF-3 or any heterodimeric form PLGF/VEGF, such as: PLGF-1/VEGF165, PLGF-2/VEGF165, PLGF-3/VEGF165 or PLGF-1/VEGF121. In fact. this latter possibility, that the protein detected in vivo be a heterodimer PLGF/VEGF, is unambiguously indicated by Failla at page 393, line 11 left hand column.

In conclusion one of ordinary skill in the art would have found in Failla no motivation to apply the angiogenic activity of PLGF-1 showed by Ziche in the attempt to cure a disease completely unrelated, as to the causes and the manifestations, to the would healing referred to by Failla.

For the same reasons it is wrong to maintain that one of ordinary skill in the art of cosmetic would have found in Failla any motivation or suggestion to try to solve the problem of natural skin aging and natural hair loss by applying the angiogenic activity of PLGF-1 showed by Ziche. Skin aging is accompanied by the same manifestation of skin scleroderma, while the reason of hair loss is not even clearly elucidated. One thing is clear. That neither skin aging nor hair loss is correlated or comparable to wound and wound-healing.

Applicants recognize that some of the above arguments have been presented previously and were not previously found persuasive. However, reconsideration is respectfully requested in view not only of these arguments, evidence and analogy, but also in view of the claim amendments to the following points of clarification, which are believed critical to resolving this aspect of the patent prosecution:

1. The first definition of "wound" in Webster's New World Dictionary, 2nd edition, is "an injury to the body in which the skin or other tissue is broken, cut, pierced, torn, etc." Those skilled in the art of medicine consider this an acute injury.

2. The states listed in claim 1 are chronic states that may result from pathological and other changes, not merely from a single wound in need of healing, which is what Failla addressed.

3. The Office action states on page 9, "As noted above, Applicants assert wounds are normally due to external agents. Claim 16 recites a state wherein skin is exposed to atmospheric aggressive agents, i.e. acidic rain, hail, or to protracted solar radiation, which may result ina skin would or skin burn, respectively. Therefore, the states recited in instant claim 16 can be considered to be a wound to the skin and/or alteration to the cutaneous tissue." This is error. A wound is an acute condition; early skin ageing is chronic, even if one of the contributing factors to the early skin ageing state is repeated exposures to some stressor that may also cause an acute wound. The key operative aspect of the third state listed is that the state is early skin ageing, which is a chronic condition and is not simply the result of a wound. Inter alia, for this reason the underlined part of the above quotation is incorrect.

As an act toward attaining greater clarity, Applicants have amended claim 16 to pluralize "exposure" to "exposures."

Based on one or more of the above bases, reconsideration and withdrawal of the above-noted rejections is respectfully requested.

Claims 30-35 stand rejected under 35 USC 103(a) as being allegedly unpatentable over Carmeliet et al.

This earlier application describes pharmaceutical compositions comprising PLGF for the prevention or treatment of an ischemic disease. First of all, ischemic diseases are not comparable to scleroderma or any other connective tissue alteration.

The Office action recognizes that Carmeliet does not disclose topical compositions comprising PLGF in the same high amount of from 0.1 mg to 10 mg per gram composition as claimed in the present claim 16, 30 or 31. However it considers that it would have been obvious for the skilled person to prepare a composition comprising the same amount of PLGF.

Applicants respectfully assert that the Office actions view concerning the teaching of Carmeliet as to the presently claimed dosage levels is based on an undue hindsight of the invention.

The amount of PLGF for unitary dosage according to the present invention is significantly higher than the amount indicated by Carmeliet, who suggests dosages of 2 to 2000 μg per Kg of body **per week**. This means, for a patient of 70 Kg, 140 μg to 140 mg per week or, for a daily unitary dosage, 20 μg to 20 mg per day.

Although an higher amount of active principle in a composition is not always capable of endowing a claim with an inventive merit, an inventive merit may recognized when this higher amount does actually reflect the optimized amount suitable to treat a specific disease. This is the case here as shown by the examples.

In fact, the examples highlight two important aspects of the treatment of the connective tissue alterations. The one is that the effect is only achieved after quite long a treatment, namely daily applications for 20 to 60 days. The second is the dose/effect dependency. Example 6 and 7 make clear that in order to see a recognizable and practically useful effect, proportionally high daily amounts of medicament have to be given. Whereas below a defined daily amount, no effect can be appreciated.

It was indeed the contribution of the present inventors to have identified the suitable PLGF-1 form and the suitable amounts, under the different circumstances, effective to treat in humans diseases and alterations of the connective tissues otherwise difficult to treat.

A further observation is that the compositions according to claims 30 and 31 comprise highly purified PLGF wherein at least 98,5% of PLGF-1 is in active dimeric and multimeric form and no more of 1,5% in inactive monomeric form. A method for purifying PLGF is disclosed for instance in the PCT international application PCT/IT02/00065 (WO-A-03/066676) cited on page 5, line 29 of the international publication corresponding to the present US application.

Carmeliet does not disclose a purified PLGF. Nor does he describe any method for obtaining the PLGF protein in active and purified form. The only part of the Careliet's application, WO-A-0156593, enabling the skilled person to obtain the necessary PLGF protein is the first paragraph

of page 5, where references in made to *Proc. Natl. Acad. Sci, USA* (1991) authored by Maglione et al. (one of the present inventors) and to US Patent No. 5,919,899 also on the name Maglione and Persico. Both references disclose the obtaining of PLGF protein as a crude bacterial extract: no renaturing of the expressed inactive monomeric form and no purification process is disclosed by both prior documents.

Furthermore, Carmeliet does not define whether the used PLGF is PLGF-1, or –2 or any other type or whether the PLGF protein is in monomeric or dimeric or multimeric form. Therefore, the very active principle used in the compositions of the prior art is different from the one according to the present application.

In conclusion, it seems that neither Carmeliet nor the other cited authors would be able to make obvious the method according to claims 30 and 31, and claims dependent thereof.

Applicants respectfully request reconsideration of this basis for rejections in view of these claim amendments, and withdrawal of this basis of rejections.

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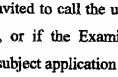
Having overcome all rejections and objections, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

The Examiner is invited to call the undersigned if clarification is needed on any aspects of this Reply/Amendment, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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